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Synthetic Sex Hormones and Infants

Treatment of pregnant women with any drugs has long been approached with caution for fear of adverse effects on the fetus, and the possibility that synthetic sex hormones might have such effects has been the subject of recurrent speculation. Recent reports have concerned oral contraceptive pills, given just before or inadvertently during pregnancy; hormonal withdrawal-type pregnancy tests; hormonal maintenance therapy for threatened or habitual abortion; and the post-coital "morning after" pill.

Virilization of the female fetus is known to be caused by large doses of progestogens given for threatened abortion[1] and vaginal adenocarcinoma may occur in the daughters of women treated with stilboesterol during pregnancy.[2] Synthetic sex hormones may possibly be teratogenic: associations have been reported between the taking of such hormones during pregnancy and spina bifida,[3] multiple congenital abnormalities,[4] oesophageal anomalies,[5] and congenital heart defects.[6] Other published reports dispute these associations.[7 8] Observations have also been made on the chromosomes of conceptuses of mothers who have used oral contraceptives. Carr[9] showed an increase in triploidy and tetraploidy in the abortuses from such women when compared with a control series. However, Rice-Wray *et al.*[10] found no structural or numerical chromosomal abnormality in live-born infants of such mothers. In this context it is important to distinguish between chromosomal and non-chromosomal abnormalities, and between abnormalities compatible with survival and those which are virtually always fatal in early embryonic life.

Very recently Janerich and his co-workers[11 12] have presented data suggesting an association between congenital limb reduction deformities and synthetic sex hormones, including oral contraceptives, given to the mother. Limb reduction deformities were defined as the absence of an arm or leg, or part thereof, including the absence of fingers and toes. One hundred and eight such cases, identified from the New York State Department of Health's Congenital Malformation Surveillance Program, were compared with 108 well matched controls. A significantly increased frequency of hormonal exposure was found among the cases. Six of the case mothers and one of the control mothers had become pregnant while taking the pill. Nine case mothers received other types of exogenous sex hormones during the relevant pregnancy (six as pregnancy supporting measures and three as withdrawal-type pregnancy tests) compared with three mothers among the controls. Of the remainder, more of the case mothers than the controls had become pregnant immediately after discontinuing oral contraceptives.

One interesting finding was that all the affected infants whose mothers had taken sex steroids by mouth during the pregnancy were male, seeming to imply a sex-specific effect on the fetus. Another was that two of the six pregnancies associated with a history of pill failure resulted in twins; only one of each pair was malformed.

The report included comment on the recent secular trends in congenital malformations and argued that if pill failure was teratogenic there should be some evidence of an epidemic of birth defects in response to the great increase in pill usage over the last decade. This does not seem to be the case. Data from the New York State Surveillance Program show a decline of about 6% in the total malformation rate over the past decade, from 11·04 to 10·38 cases per 1,000 births. However, during the same period the rate of limb reduction defects increased by 33%, from 0·15 to 0·20 per 1,000 births.In England and Wales there has been an increase in the incidence of notified malformations between 1968 and 1971—which may represent more complete reporting—but no consistent change in any particular abnormality.[13]

The recent report of the Royal College of General Practitioners on Oral Contraceptives and Health suggested from substantial data that there was no demonstrable adverse effect of the pill on the outcome of subsequent pregnancies.[14] It added the caution that more data and a detailed analysis of reported abnormalities were desirable "before this conclusion can be asserted with confidence."

Janerich *et al.* considered various explanations for the association they found. The first was that it was causal, which was supported by the sex-specificity of the observations and by the reported secular trends in limb reduction defects. The second was that the association was with some underlying maternal disorder: that the mother was at high risk of bearing infants with a limb reduction defect and of experiencing a breakthrough pregnancy while on the pill, or presenting symptoms that indicated the need for hormonal support. To these may be added the remote possibility that the exogenous hormones effectively supported an abnormal pregnancy which would otherwise have been aborted.

What are the practical implications of this and other reported associations between sex steroids and congenital

anomalies? Firstly, the findings require confirmation or refutation from elsewhere. Secondly, if the association described by Janerich *et al.* is causal the increased risk (calculated at 4·7) is small; exposure to the pill may constitute an extra insult in an otherwise predisposed fetus.[15] However, in each instance where sex steroids are used the risk-benefit ratio should be critically assessed. As others have stressed, there is little justification for the continued use of withdrawal-type pregnancy tests when alternative methods are available;[12] and it is prudent to be certain of the absence of pregnancy before starting a woman on oral contraceptives.[16] There is often a delay of two or three months before pregnancy occurs in women who stop taking oral contraceptives in order to become pregnant.[14] If the finding of an association is confirmed between congenital anomalies and oral contraceptives taken recently before or after conception this delay may prove to be fortunate. However, some may consider it wise to recommend that an intending mother should use an alternative method of contraception for a couple of months between stopping the pill and trying to become pregnant. There is no evidence in the data available that oral contraceptives taken up to a few months before pregnancy increase the risk of malformation in the infant.

[1] Wilkins, L., *Journal of the American Medical Association*, 1960, **172**, 1028.
[2] Herbst, A. L., *et al.*, *New England Journal of Medicine*, 1972, **287**, 1259.
[3] Gal, I., Kirman, B., and Stern, J., *Nature*, 1967, **216**, 83.
[4] Nora, J. J., and Nora, A. H., *Lancet*, 1973, **1**, 941.
[5] Oakley, G. P., Flynt, W. J., and Falek, A., *Lancet*, 1973, **2**, 256.
[6] Levy, E. P., Cohen, A., and Fraser, F. C., *Lancet*, 1973, **1**, 611.
[7] Laurence, M., *et al.*, *Nature*, 1971, **233**, 495.
[8] David, T. J., and O'Callaghan, S. E., *Lancet*, 1974, **1**, 1236.
[9] Carr, D. H., *Canadian Medical Association Journal*, 1970, **103**, 343.
[10] Rice-Wray, E., Marquez-Monter, H., and Gorodovsky, J., *Contraception*, 1970, **1**, 81.
[11] Janerich, D. T., Piper, J. M., and Glebatis, D. M., *Lancet*, 1973, **2**, 96.
[12] Janerich, D. T., Piper, J. M., and Glebatis, D. M., *New England Journal of Medicine*, 1974, **291**, 697.
[13] Department of Health and Social Security, on *The State of the Public Health*, London, H.M.S.O., 1972.
[14] Royal College of General Practitioners, *Oral Contraceptives and Health*. London, Pitman, 1974.
[15] Balci, S., *et al.*, *Lancet*, 1973, **2**, 1098.
[16] Nora, J. T., and Nora, A. H., *New England Journal of Medicine*, 1974, **291**, 732.

Bulletin on Medical Care

The *British Medical Bulletin*, which is published by the British Council, first appeared some 30 years ago with the object of presenting recent advances in medicine with special emphasis on the British contribution. Each of the three numbers a year is usually focused on a single subject. In the current year these have been radioimmmune assay and saturation analysis; development and regeneration in the nervous system; and research in medical care. The usual practice is to appoint a committee and chairman to plan each number of the *Bulletin*, together with one or more scientific editors. The level of scholarship is high and the *Bulletin* is definitely one of the "heavies." Indeed, only a polymath could be expected to read it through regularly, but the medical scientist seizes upon it with joy when it deals with some special interest of his own, for he knows that it will provide him with a clear and up-to-date picture of the march of events such as no single individual would be likely to be able to produce.

The current number on research in medical care will be of interest to most readers of the *B.M.J.* It has always been a mystery that though scientists such as Watson-Watt had developed operational research as a major instrument and contribution to victory in the second world war and Zuckerman and others had introduced the idea of the "think tank" these techniques were at first almost completely neglected in the setting up of the National Health Service. Operational research has been defined[1] as "the application of scientific methods to the sort of problems that confront executive authorities," and such methods are obviously needed in a great organization like the N.H.S. Happily a change has occurred, and between 1962 and 1972 annual expenditure on research into the health services increased from a few hundred thousand pounds to £10 million. Cochrane[2] has said that the problem of evaluation is the first priority of the N.H.S., and much of this number deals with the evaluation of health activities. The field covered is wide and so full of opportunities for research that it should be most attractive to recent graduates in medicine. The problems are different from those usually studied in medical research laboratories, as the factors in the equation are usually manifold and the subject of inquiry is man himself and his behaviour. Methods employed include epidemiology, statistics, psychology, social science, economics, and administration, and at a time when much of clinical science has lost its relevance and impetus few fields offer a more rewarding return for effort.

[1] Bailey, N. T. J., in *Medical Surveys and Clinical Trials*, 2nd edn., p. 164, ed. L. J. Witts. London, Oxford University Press, 1964.
[2] Cochrane, A. L., *Effectiveness and efficiency: random reflections on health services*, p. 25. Oxford, Nuffield Provincial Hospitals Trust, 1972.

More Facts on Vinyl Chloride and Cancer

In an earlier leading article[1] we reported that vinyl chloride, which is used to make the valuable plastic polyvinylchloride, had apparently led to three cases of angiosarcoma of the liver among workmen in one U.S. plant. Only about 25 instances of this tumour are found annually in the entire population of the U.S.A. Thirteen cases of angiosarcoma of the liver have now been reported among American vinyl chloride workers, and two of them had coexisting angiosarcomas of other tissues.[2] Instances of liver angiosarcoma in vinyl chloride workers have also been found in West Germany, Sweden, the United Kingdom, and Norway. Most, but not all, of the affected men had worked on the polymerization process in which there are intermittent high atmospheric levels of exposure to vinyl chloride. The mean age of the American cases was 48·2 years (range 36-60 years) and the latent interval between first exposure and the diagnosis of cancer ranged from 12 to 29 years. Heath *et al.*[2] calculated that this represented a 400-fold excess of angiosarcoma of the liver in the population studied. The relatively young mean age at which the tumours developed and the great increase in incidence of the disease leave little room for doubt that angiosarcoma of the liver among vinyl chloride workers is a new occupational disease. Even if there were no further contamination with vinyl chloride it is probable that further instances will occur in the workers who have already been exposed.

B. F. Goodrich and Co., the firm from which the original reports emerged, have now identified[3] seven cases of angiosarcoma of the liver and four of non-malignant hepatic disease in their workforce. This firm has described its programme[4] for the detection of liver disease and angiosarcoma in vinyl chloride workers. The initial screen consisted of either 12 or 18 simple tests on the blood of the 1,183 workpeople, in-